REMARKS

The Office action dated January 19, 2007 is acknowledged. Claims 1-16 are pending in the instant application. According to the Office action, each of these claims has been rejected. By the present Office Action response, claims 1, 5, 8, 9, 12, 14 and 16 have been amended and claim 7 has been canceled. It is noted that the subject matter of claim 7 has been incorporated into claim 1, namely, that the non-oily emulsion is a mixture of lecithin, bile salts and cholesterol in water. Claim 5 has been clarified to recite that the molecular weight is 7000 Dalton, rather than 7000 kDa, support for which may be found in the specification at paragraph [000014]. The amendment to claim 12 is simply a correction of a minor informality. Reconsideration is respectfully requested in light of the amendments being made hereby and the arguments made herein. No new matter has been added.

Claim Objections

The Examiner has objected to claim 14 for use of the acronym "TTS." Claim 14 has been amended to use the full terminology of this acronym. Claims 11-13 and 16 have been objected to due to inconsistencies between the terms "organic sulfur" (claim 11) and "organic sulphur" (claim 16). This inconsistency has been corrected. Withdrawal of these objections is therefore respectfully requested.

Rejection of Claims 1, 2, 4-6, 11 and 13-15 under 35 U.S.C. 102(a) & (e)

Claims 1, 2, 4-6, 11 and 13-15 have been rejected under 35 U.S.C. 102(a) & (e) as being anticipated by U.S. Patent No. 6,444,234 (Kirby, et al.). The Examiner states that Kirby, et al. teaches discloses a composition for transdermal administration of at least one therapeutically active compound (i.e., polypeptide) or nutrient (i.e., vitamins), the

composition comprising one item selected from the group consisting of at least one therapeutically active compound such as antibiotic drugs and at lest one nutrient and a non-oily emulsion (i.e., cholesterol), wherein the polypeptide has a molecular weight of 500 D and higher (which overlaps with the range of up to 7000 kDa of claim 5) and further comprising an organic sulfur compound (i.e., methylsulfonylmethane), wherein the composition for transdermal administration of active substance which is nutrients and/or medications are useful as a cream, gel, lotion, ointment and patch (col. 1, 5-11, 15, 31 and 32). Therefore, the Examiner concludes that the device of Kirby, et al. discloses the present invention as claimed in claims 1, 2, 4-6, 11 and 13-15.

The Applicant submits that claim 1 has been amended, as set forth above, to define the non-oily emulsion as being a mixture of lecithin, bile salts and cholesterol in water, which had originally been set forth in claim 7 (now cancelled). Kirby, et al. fails to disclose this feature of the present invention, as acknowledged by the Examiner in the Office action on page 5, lines 12-15. Therefore, Kirby, et al. clearly fails to teach or otherwise disclose every limitation of the present invention as set forth in independent claim 1 and therefore fails to anticipate the present invention. Withdrawal of this rejection is respectfully requested.

Rejection of Claims 1-16 Under 35 U.S.C. 103(a)

Claims 1-16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kirby, et al., taken with U.S. Patent No. 5,759,445 (Yamamoto, et al.), Guo, et al. (Drug Deli. Vol. 7, No. 2, pp. 113-116, 2000) and Thorand, et al. (Southeast Asian J. Trop. Med. Public Health, Vol. 24, No. 4, pp. 624-630, 1993). The Examiner states that Kirby, et al. discloses, as discussed above, the present invention but does not teach the

use of non-oily emulsion which is a mixture of lecithin, bile salt and cholesterol with the specific ratio and amount disclosed in the present claims, and the use of a nutrient which is an ionic compound – the ionic compound being a metal ion. The Examiner argues that Guo, et al. discloses a study of transdermal delivery of insulin (therapeutically active compound and/or peptide) in mice by using lecithin vesicles as a carrier. The Examiner notes that the Guo, et al. study was undertaken to characterize the preparation of flexible lecithin vesicles containing insulin and to assess the enhancing effect of these flexible vesicles on the transdermal delivery of hydrophilic proteins or polypeptides. The Examiner states that the reference concludes by stating flexible vesicles may become a promising carrier for transdermal delivery of hydrophilic polypeptides (e.g., Abstract and Discussion).

The Examiner further states that the secondary reference of Yamamoto, et al. discloses an aqueous dispersed solution, which comprises the steps of evaporating an organic solvent from a mixture prepared by adding cholesterol, lecithin, a surfactant and a neutral lipid, and/or a cholesterol ester in the organic solvent in a specific range of the concentration ratio. The preferred ratio of the sum of the cholesterol and cholesterol ester to the lecithin is from 1:1 to 1:2, a weight ratio of the neutral lipid to the lecithin is from 1:10 to 1:5, and a concentration of the lecithin is not more than 1,000 mg/dl when the lecithin is finally dispersed in a water or buffer (see, e.g., Summary of the Invention and claim 4). Thus, the Examiner states that utilizing the mixtures of non-oily emulsion of lecithin, bile salt and cholesterol is a choice procedure as pointed out by Yamamoto, et al., and as such, use of non-oily emulsion which is a mixture of lecithin, bile salt and cholesterol would be obvious in the art since it is reasonably expected that use of non-

oily emulsion such as lecithin would have resulted as a promising carrier for transdermal delivery of hydrophilic polypeptides as taught by Guo, et al. Thus, the Examiner concludes that one of ordinary skill in the art would have been motivated to employ a composition for transdermal administration of the primary reference because such features are known or suggested in the art, as seen in the secondary reference, and including such features (i.e., use of non-oily emulsion which is a mixture of lecithin, bile salt and cholesterol) into a composition for transdermal administration of at least one therapeutically active compound (polypeptide) or nutrient (vitamins), said composition comprising one item selected from the group consisting of at least therapeutically active compound such as antibiotic drugs and at least one nutrient and a non-oily emulsion, wherein the polypeptide has a molecular weight of 500D and higher and further comprising an organic sulfur compound (MSM), wherein the composition for transdermal administration of active substance which is nutrient and/or medications are useful as a cream, gel, lotion, ointment and patch.

The Examiner still further states that Thorand, et al. demonstrate that the administration of iron (metal ion) supplement is an effective intervention in treating anemia caused by iron deficiency. Thus, the reference shows the administration of at least one therapeutically active compound and said at least one nutrient is an ionic compound, wherein the ionic compound is a metal ion (i.e., iron as a nutrient).

The Applicant respectfully submits that to establish a *prima facie* case of obviousness, three basic criteria must be met, as set forth in M.P.E.P. § 2142. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third,

the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Applicant respectfully disagrees with the Examiner's conclusion set forth in the Office action. By way of a brief summary of the present invention, it is provided that therapeutically active polypeptides or ionic nutrients can be administered through the human skin if a non-oily emulsion of lecithin, bile salts and cholesterol in water is utilized. Despite considerable effort, such an invention simply has not yet been achieved. In particular, the prior art has not yet achieved providing a reliable system for transdermal administration of polypeptides or ions which would enable transdermal administration of insulin to a diabetic patient at a therapeutically sufficient rate and without providing a risk of hypoglycemia, as noted in paragraph [000029] (and elsewhere) of the present specification. The present invention may provide the basis for a system by which numerous diabetic patients would benefit. The presently claimed invention achieves this goal. In short, the prior art fails to teach or make obvious the utility of a non-oily emulsion which is a mixture of lecithin, bile salts and cholesterol in water.

The Applicant submits that Kirby, et al. teaches compositions for rapid and non-irritating transdermal delivery of pharmaceutically active agents and provides a formulation which includes:

(A) at least one solvent in which the active agent is soluble;

(B) at least one solvent modifier having common structural features as that of the active agent and comprising an ethylenically unsaturated polar group;

(C) at least one metabolizable solute modifier;

(D) at least one source of cellular activation energy; and

(E) at least one skin stabilizer (col. 7, lines 3-21).

Kirby, et al. further specifies that the solvent (A) may be any of the solvents normally used for medicaments, cosmetics, nutrients or other active agents to be transdermally delivered (col. 10, lines 5-7). However, the solvent system is generally non-aqueous (col. 10, line 17). The solvent modifier (B) is preferably methylsulfonylmethane (MSM) (col. 11, lines 11-14), and the solute modifier (C) may be, for example, cholesterol (col. 11, line 51).

The Applicant submits that a crucial aspect of the formulation of Kirby, et al. is the presence of Foskolin or other source of cellular energy (D), namely, induction of cAMP or cGMP (Abstract). The source of cellular activation energy may be selected from the group consisting of ATP (claim 1), ADP, NADH, and $FADH_2$ (col. 12, lines 39-42), Forskolin, Colforsin and coleonol (col. 12, lines 52-57), methyl xanthines, Saikogenin, Saikosaponin, *Angelacie dahuricae* radix, phelopterin, oxypeucedanin, acetylcholine, cytidene, diphosphocholine and ascorbic acid (Vitamin C) (col. 12, lines 58-65). The source of cellular activation energy shall minimize energy-negative reactions which could lead to sensitization, ACD or anaphylaxis (col, 12, lines 28-35). It is further submitted that one skilled in the art would clearly understand from the disclosure of Kirby, et al. in col. 6, lines 20-30; col. 6, line 66 – col. 7, line 18; col. 7, lines 22-47; col. 9, lines 43-45 and claim 1 that the source of cellular activation energy is an essential component of the liquid carrier composition for the transdermal delivery of a medicament, as disclosed therein.

To the contrary, the composition for transdermal administration of a

therapeutically active compound or nutrient according to the present invention does not contain a source of cellular activation energy. Moreover, one skilled in the art can not and would not infer from Kirby, et al.'s disclosure that a source of cellular activation energy may be omitted from the liquid carrier composition without impairing the desired transdermal delivery of a medicament. Thus, the Applicant submits that Kirby, et al. does not make a formulation obvious which does not contain a source of cellular activation energy.

In addition, Kirby, et al. teach in column 16, lines 10-30 that the composition of the Stock Delivery System (SDS) is primarily (i.e., above 90%) composed of alcohols (i.e., propylene glycol and either ethanol, i-propanol or sec-butanol). These alcohols are generally considered irritant to the human skin, but may cause transdermal delivery of various molecules. Under these conditions, (i.e., Example 13; column 13, line 65 – column 42, line 50), an attempt was made to transdermally deliver a relatively small molecule (morphine sulphate, 669 Dalton) using Franz cells and hairless rat skin (which one skilled in the art would recognize as being more permeable than human skin). Nevertheless, according to the results (Tables 10-13, and Figures 1 – 4), it took more than 20 hours to detect a noticeable flux of morphine across the rat skin. The Applicant respectfully submits that the present invention still does not contain any of the aforementioned alcohols of Kirby, et al. However, the present invention permits delivery of large molecules (e.g., insulin, 5800 Dalton) to humans in-vivo, whose skin is less permeable than the rat skin tested in Kirby, et al., within just a few hours.

Kirby, et al. may teach that the solute modifier may be methylsulfonylmethane or cholesterol. Kirby, et al. also discloses that the topical formulation includes

methylsulfonylmethane as a metabolizable solute modifier and phosphatidyl choline as a solute modifier in a special embodiment (col. 7, lines 23-47). However, Kirby, et al. fails to disclose a non-oily emulsion which is a mixture of lecithin, bile salts and cholesterol in water, as acknowledged by the Examiner. Since non-aqueous solvent systems are preferred pursuant to Kirby, et. al. (col. 10, line 17), the Applicant submits that the reference does not teach or suggest modifying the formulations disclosed therein to obtain a non-oily emulsion of lecithin, bile salts and cholesterol in water and therefore one skilled in the art would not have been motivated to modify the teachings of Kirby, et al. in accordance with the present invention. For these reasons, it is respectfully submitted that Kirby, et al., fails to anticipate or make obvious the presently claimed invention since the reference does not make obvious a formulation that does not contain a source of cellular activation energy and/or is void of an alcohol selcted from the group consisting of propylene glycol, ethanol, i-propanol and sec-butanol.

In addition, Guo, et al. teach the utility of specifically designed flexible vesicles for transdermal delivery of insulin. These specific vesicles comprise sodium cholate, which is a detergent, that may be incorporated into the lipid bilayer of the vesicles to improve elasticity of the vesicles (p. 113, right column, 2nd paragraph). Turning to Figure 3 in the Guo, et al. article (page 115, right column), it appears that conventional (i.e., rigid) vesicles can hardly reduce the blood glucose concentration in mice to a larger extent than the mere application of an insulin solution or saline solution (i.e., –▲– vs. –X– and –▲– vs. –*–). Comparing the effect of conventional vesicles with the effect of the flexible vesicles on blood glucose concentration of treated mice (i.e., –▲– vs. –♦–), it becomes evident that the improved transdermal delivery obtained by Guo, et al. can be

attributed to the use of sodium cholate for preparing insulin-containing vesicles rather than by a mechanism in accordance with the present invention.

However, the composition of the present invention does not contain sodium cholate, but rather cholesterol. Although cholesterol and sodium cholate are structurally similar molecules, Guo, et al. does not provide any motivation or teaching (or any other information) that replacing sodium cholate with cholesterol would also yield flexible vesicles displaying improved transdermal delivery of insulin. In addition, the Applicant notes that it should be appreciated that the skin of mice is highly permeable and therefore an extrapolation from mice to humans, insofar as transdermal delivery is concerned, is not always proper or reliable. Clearly, Guo, et al. fail to make up for the aforementioned deficiencies of Kirby, et al.

The Applicant further submits that the formulations of Kirby, et al. are not vesicular preparations. Kirby, et al. teach the preparation of emulsions, but emulsions do not necessarily have to comprise vesicles, i.e., liposomes, comprising a lipid bilayer and entrapping insulin in the lumen of the vesicles. Specific methods are required for preparation of liposomes. Neither the formulations of Kirby, et al., nor the non-oily emulsion of the present invention, are liposomal preparations.

Therefore, the Applicant submits that one skilled in the art would not have combined the disclosures of Kirby, et al. and Guo, et al. and reasonably expect to successfully improve transdermal delivery of insulin in accordance with the present invention, nor would every feature of the present invention be taught or disclosed. On the other hand, the Applicant submits that if one were to combine the teachings of these two references, the skilled artisan would either replace cholesterol as the solute modifier

with sodium cholate in a formulation according to Kirby, et al., or alternatively would supplement the flexible vesicles of Guo, et al. with a source of cellular activation energy. Neither combination would yield the presently claimed invention. Moreover, it would remain enigmatic as to whether an improved efficacy in transdermal drug delivery could be obtained, since if transdermal administration of insulin by the flexible vesicles in fact occurs through the interstices of the stratum corneum (i.e., first proposed mechanism, page 116, left col., last paragraph) then the addition of a source of cellular activation energy would apparently not affect the transdermal drug delivery since no energy consuming cellular mechanisms would be involved in the particle's transdermal penetration. Clearly, the combination of teachings of Kirby, et al. and Guo, et al. fails to make the presently claimed invention obvious.

The Applicant still further submits that Yamamoto, et al. teach an aqueous lipid-dispersed solution having a dispersion form and particle size which are similar to those of serum lipids. The lipid-dispersed solution is obtained by evaporating an organic solvent from a mixture prepared by adding cholesterol, a phospholipid, bile acid salts and a neutral lipid and/or cholesterol ester to the organic solvent.

The Applicant notes that the aqueous dispersed solution according to Yamamoto, et al. is not intended for transdermal drug delivery. The aqueous dispersed solution is merely a standard solution for determining lipid levels in sera. Yamamoto, et al. does not indicate or teach at all that the standard solution may be employed for transdermal drug delivery. The Applicant further notes that the non-oily emulsion of the present invention does not contain a neutral lipid or a cholesterol ester. Yamamoto, et al. fail to indicate that the neutral lipid or cholesterol ester may be omitted from the preparation. Thus,

even if one skilled in the art were to combine Kirby, et al.'s disclosure with that of Yamamoto, et al., the skilled artisan would not arrive at a non-oily emulsion made of lecithin, bile salts and cholesterol in water, but without any source of cellular activation energy (as discussed above).

Regarding Thorand, et al., the reference pertains to the bioavailability of iron but does not relate to transdermal administration of iron. Thorand, et al. solely disclose iron tablets and therefore pertains to an oral administration of iron. Therefore, Thorand, et al. does not provide any information or teaching toward the transdermal administration of iron. In turn, the present invention can not have been made obvious even if the combination of references included the teachings of Thorand, et al.

It is therefore respectfully submitted that the present invention defined in the presently amended claims is patentably distinguishable over the combination of prior art teachings under 35 U.S.C. 103(a). Based on the aforementioned differences, each and every element of the present invention recited in claims 1-6 and 8-16 are not set forth in the Kirby, et al., alone or in combination with any of the cited secondary references. Moreover, one skilled in the art would not be motivated to combine said references or to modify Kirby, et al. to arrive at the presently claimed invention. Therefore, the Applicant respectfully requests that this rejection be withdrawn.

Conclusion

For the foregoing reasons, it is believed that the present application, as amended, is in condition for allowance, and such action is earnestly solicited. Based on the foregoing arguments, amendments to the claims and deficiencies of the prior art references, the Applicant strongly urges that the obviousness-type rejection and

anticipation rejection be withdrawn. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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